

Attorney Docket No.: DEX-0079  
Inventors: Burczak and Wilkinson  
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AB  
and  
cancer, a decrease in the measured levels of PLA<sub>2</sub> over time is indicative of remission or response to therapy of the cancer, and no change in the measured levels of PLA<sub>2</sub> over time is indicative of stabilization of the cancer.

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**REMARKS**

Claims 1-15 are pending in the instant application. Claims 1-8 and 10-15 have been rejected. Claim 9 has been objected to. Claims 1, 6, 10 and 13 have been amended. Claims 4 and 9 have been canceled. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

**I. Priority**

In accordance with the Examiner's suggestion, the specification has been amended to include in the first sentence following the title reference to the prior filed international application of the instant application.

However, Applicants respectfully disagree with the Examiner's suggestion that the specification of U.S. Patent Application Serial No. 09/111,938, filed July 8, 1998 is not supportive of the full

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scope of the claims of the instant specification.

At the outset, it is respectfully pointed out that the instant claims are drawn to methods of monitoring and diagnosing cancer in patients, not "subjects" as suggested by the Examiner. Support for methods of monitoring and diagnosing cancer in patients is provided throughout the entire 09/111,938 specification. As taught at page 5, lines 26-29 of 09/111,938, it is a preferred embodiment wherein the method is used for monitoring human patients specifically.

Further support for use of the term "patient" can be found in U.S. Provisional Application Serial No. 60/075,504 filed February 23, 1998 from which the instant application also claims priority.

Accordingly, Applicants believe that for comparison with the prior art, the filing date used for the instant application should be February 23, 1998.

## **II. Rejection of Claims 1-5 and 10-12 under 35 U.S.C. 112, second paragraph**

Claims 1-5 and 10-12 have been rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

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With respect to claim 1, the Examiner suggests that the correlation statement does not match with the preamble statement. Specifically, the Examiner suggests that the preamble is directed to a method of monitoring cancer that has not metastasized for the onset of metastasis while the correlative statement is directed to determining that one has a metastatic cancer.

With respect to claim 10, the Examiner suggests that the preamble recites a method for diagnosing ovarian or testicular cancer, while the correlative statement is directed to all cancers.

Accordingly, in an earnest effort to advance the prosecution of this case, Applicants have amended these claims so that the preamble and correlative statement match. Specifically, claim 1 has been amended to state in the correlative statement that elevated levels of  $PLA_2$  in a sample of bodily fluid are indicative of onset of metastasis of the cancer. Claim 10 has been amended to specify testicular and ovarian cancer in the correlative statement.

Withdrawal of these rejections under 35 U.S.C. 112, second paragraph is respectfully requested in light of these amendments.

### III. Rejection of Claims 1-3, 5 and 13-15 under 35 U.S.C. 102(e)

Claims 1-3, 5 and 13-15 have been rejected under 35 U.S.C. 102(e) as being anticipated by Schmidt et al. (U.S. Patent

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5,747,264). The Examiner suggests that U.S. Patent 5,747,264 discloses methods for diagnosing, monitoring progression, remission or recurrence of prostate cancer (col. 1, line 65 - col. 2, line 8) and teaches elevated levels of mRNA encoding PLA<sub>2</sub> are present in prostate cancer (col. 1, lines 48-59). The Examiner suggests that the detection of onset of metastasis is considered to be an obvious species of "monitoring progression".

Accordingly, in an earnest effort to advance the prosecution of this case, Applicants have amended the claims 1 and 13 to specify that an enzyme level cut-off of 4.5 ng/ml is used when measuring PLA<sub>2</sub> in sample of bodily fluid. Support for this amendment is found in the claims as originally filed and in the specification at page 12, lines 17-22, and page 13, lines 7-15 and page 14, lines 8-13. Claim 4 has been canceled in light of this amendment.

As acknowledged by the Examiner at page 6 of the Office Action, claims drawn to use of this enzyme level cut-off to measure PLA<sub>2</sub> are free of the prior art. Accordingly, withdrawal of this rejection under 35 U.S.C. § 102(e) is respectfully requested in light of the amendments to the claims.

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IV. Rejection of Claims 1, 2, 3, 5-8, 10, and 12-15 under 35  
U.S.C. 103

Claims 1, 2, 5-7, 13 and 14 have been rejected under 35 U.S.C. 103 as being unpatentable over Yamashita et al. [a] (Clin Chim Acta 1994 228:91-99) in view of Yamashita et al. [b] (Surgery 1995 117:601-608). The Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have made a method for monitoring the onset of metastasis or for diagnosing metastasis in view of the teachings of these references. The Examiner suggests that one would have been motivated to use the teachings of Yamashita [a] to devise such a method because of the long felt need for methods to differentiate between patients with metastatic cancer from those without metastatic cancer. Further, the Examiner suggests that one would have had a reasonable expectation of success because the number of different cancers that were studied and Yamashita [a] also teaches that the increase in serum M-PLA<sub>2</sub> levels are due to production and secretion of M-PLA<sub>2</sub> by cancer cells, indicating that increased secretion of PLA<sub>2</sub> is due to an increase in tumor cell number.

Claims 1, 3, 6, 8, 10, 12 and 15 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Yamashita et al. [a] in

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view of Yamashita et al. [b] and further in view of Roitt et al. or Holme et al. The Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the assay of Yamashita using the teaching of Roitt and Holme relating to ELISAs to develop an ELISA method. The Examiner suggests that one would have been motivated to substitute the ELISA method for the radioimmunoassay method in order to avoid the use of radioisotopes, which are known to be hazardous and difficult to dispose.

With respect to the rejection of claims 1, 2, 3, 5, 6, 7, 8, 10, 12, 13, 14 and 15, it is respectfully pointed out that claims 1, 6 and 13 have been amended to specify that an enzyme level cut-off of 4.5 ng/ml is used to measure PLA<sub>2</sub> in sample of bodily fluid. As discussed in Section III, *supra*, claims drawn to use of this enzyme level cut-off to measure PLA<sub>2</sub> have been acknowledged by the Examiner to be free of the prior art. Accordingly, this amendment overcomes the rejection of claims 1, 6 and 13 and claims dependent therefrom under 35 U.S.C. § 103.

Applicants respectfully traverse the rejection of claims 10 and 12 under 35 U.S.C. § 103(a) as being unpatentable over the teachings of Yamashita et al. [a] in view of Yamashita et al. [b] and further in view of Roitt et al. or Holme et al. Nowhere do any

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of these references teach or suggest detection of PLA<sub>2</sub> as a means for diagnosing ovarian or testicular cancer. Accordingly, the combination of references fails to provide either the requisite reasonable expectation of success or suggestion or teaching of all claim limitations to render claims drawn to a method of diagnosing ovarian or testicular cancer in a patient via detecting levels of PLA<sub>2</sub> in a sample of the patient obvious. See MPEP 2143.

Thus, withdrawal of these rejections under 35 U.S.C. § 103(a) is respectfully requested.

#### V. Objection to Claims 4 and 9

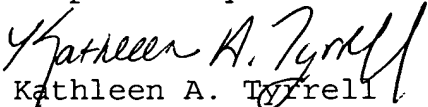
Claims 4 and 9 have been acknowledged to be free of the art. However, these claims have been objected to as depending from a rejected claim. Accordingly, in earnest effort to advance the prosecution of this case, independent claim 1 and independent claim 6, from which claims 4 and 9 ultimately depend, respectively, have been amended to include the limitations of claims 4 and 9, respectively. Claims 4 and 9 have been canceled in light of these amendments. Withdrawal of this objection is respectfully requested in light of these amendments.

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## VI. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Respectfully submitted,  
  
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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification:

At page 1, please replace the paragraph at lines 5 through 10 with the following:

~~--This application is a continuation of application Serial No. 09/175,504, filed October 20, 1998 which is a continuation-in-part of application Serial No. 09/111,938, filed July 8, 1998, pending, which is a continuation-in-part of provisional application Serial No. 60/075,504, filed February 23, 1998.~~ This application is the National Stage of International Application no. PCT/US99/03170, filed February 12, 1999, which is continuation of U.S. Application Serial No. 09/175,504, now abandoned, filed October 20, 1998, which is a continuation-in-part of U.S. Application Serial No. 09/111,938, now abandoned filed July 8, 1998, which claims the benefit of priority from U.S. Provisional Application Serial No. 60/075,504, filed February 23, 1998. --

In the Claims:

Please cancel claims 4 and 9.

Please amend the claims as follows:

1. (amended) A method of monitoring a cancer in a patient

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*is not known to have metastasized*  
which ~~has not~~ metastasized for the onset of metastasis comprising:

(a) identifying a patient having a cancer that is not known to have metastasized;

(b) periodically analyzing a sample of bodily fluid from the patient for PLA<sub>2</sub>; and

(c) detecting levels of PLA<sub>2</sub> *at or above* with an enzyme level cut-off ~~of 4.5 ng/ml~~, in the sample of bodily fluid obtained from the patient wherein <sup>SAID</sup> ~~elevated~~ levels of PLA<sub>2</sub> in a sample of bodily fluid are indicative of ~~a cancer which has metastasized~~ onset of metastasis of the cancer.

6. (amended) A method of diagnosing a metastatic cancer in a patient comprising:

(a) obtaining a sample of biological fluid from a patient; and

(b) detecting the level of PLA<sub>2</sub> with an enzyme level cut- *Some as above*  
off of 4.5 ng/ml, in a sample of biological fluid wherein elevated levels of PLA<sub>2</sub> in the sample are indicative of metastatic cancer.

10. (amended) A method of diagnosing ovarian or testicular cancer in a patient comprising:

(a) obtaining a sample of biological fluid from a patient; and

(b) detecting levels of PLA<sub>2</sub> in the sample; wherein *epithelial of testicular*

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elevated levels of PLA<sub>2</sub> in the sample are indicative of ovarian or testicular cancer.

13. (amended) A method of monitoring progression, remission, response to therapy and stabilization of prostate, breast, ovarian or testicular cancer in a patient comprising measuring PLA<sub>2</sub> levels with an enzyme level cut-off of 4.5 in biological fluids obtained from a patient at selected times wherein an increase in the measured levels of PLA<sub>2</sub> over time is indicative of progressive cancer, a decrease in the measured levels of PLA<sub>2</sub> over time is indicative of remission or response to therapy of the cancer, and no change in the measured levels of PLA<sub>2</sub> over time is indicative of stabilization of the cancer. True?